Clinical Efficacy, Tolerability, and Cost Savings Associated with the Use of Open-Label Metronidazole Plus Ceftriaxone Once Daily Compared with Ticarcillin/Clavulanate Every 6 Hours as Empiric Treatment for Diabetic Lower-Extremity Infections in Older Males

Patrick G. Clay, PharmD,[1,2] Maqual R. Graham, PharmD,[1,3] Cameron C. Lindsey, PharmD,[1,3] Kenneth C. Lamp, PharmD,[4] Collin Freeman, PharmD,[5] and Alan Glaros, PhD[6]

[1]Department of Pharmacy Practice, University of Missouri–Kansas City School of Pharmacy, [2]Kansas City Free Health Clinic, [3]Department of Pharmacy Services, Veterans Affairs Medical Center, Kansas City, Missouri, [4]Cubist Pharmaceuticals, Inc., Halstead, Kansas, [5]VHA Inc., Shawnee, Kansas, and [6]Department of Dental Public Health and Behavioral Science, University of Missouri–Kansas City School of Dentistry, Kansas City, Missouri

ABSTRACT

Background: Patients with diabetes mellitus, particularly those with poor glucose control, commonly experience various medical complications related to the disease (eg, renal impairment, decreased peripheral vascular circulation, suppressed immune function). Infections of the lower extremities can range from superficial cellulitis to ulcerative, deep soft-tissue infections to osteomyelitis that necessitates some degree of amputation.

Objective: This study compared the efficacy, tolerability, and cost differences associated with the use of metronidazole plus ceftriaxone (MTZ/CTX) given once daily with those of ticarcillin/clavulanate potassium (T/C) given every 6 hours in hospitalized older males with diabetic lower-extremity infections.

Methods: This prospective, open-label study was conducted at a Veterans Affairs Medical Center. Male patients with diabetes and a lower-extremity infection were randomized to receive MTZ/CTX 1 g once daily or T/C 3.1 g every 6 hours. Treatment success was determined at 96 hours or on discontinuation of antibiotic. Success was measured in terms of body temperature <38.3°C (100.6°F), normalization of the finger-stick blood sugar concentration, improvement in wound staging, or a white blood cell count <10,000 cells/mm^3. Medication acquisition costs per treatment arm were calculated and compared.

Results: Seventy patients were enrolled in the study (36 MTZ/CTX, 34 T/C). The study population had a mean (SD) age of 63.8 (10.8) years, a duration of diabetes of 12.4 (9.1) years, 0.5 (0.7) diabetes-related comorbidities, and an initial creatinine clearance of 67.1 (26.0) mL/min. There were no significant differences between groups at randomization. At 96 hours, treatment success was achieved in 31 (86%) patients in the MTZ/CTX group, compared with 28 (82%) patients in the T/C group (P = NS). Twenty-six patients were considered successfully treated on the final day of therapy in both the MTZ/CTX group (72%) and the T/C group (76%) (P = NS). There were no significant differences in primary or secondary measures of success between the 2 groups. No single or multiple baseline factors predicted treatment success or failure. No patient experienced adverse events considered related to study medication. MTZ/CTX was associated with savings of $61.06 per hospital admission, or $2198.05 for all patients who received this combination.

Conclusion: In this population of older males, once-daily MTZ/CTX was as well tolerated and effective as T/C in the treatment of diabetic lower-extremity infections and was associated with reduced institutional costs. (*Am J Geriatr Pharmacother.* 2004;2:181–189) Copyright © 2004 Excerpta Medica, Inc.

Key words: ceftriaxone, metronidazole, ticarcillin/clavulanate, diabetes, lower-extremity infection.

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INTRODUCTION

Patients with diabetes mellitus, particularly those with poor glucose control, commonly experience various medical complications related to the disease (eg, renal impairment, decreased peripheral vascular circulation, suppressed immune function). Infections of the lower extremities (often referred to as diabetic foot infections) can range from superficial cellulitis to ulcerative, deep soft-tissue infections to osteomyelitis that necessitates some degree of amputation in 50% to 62% of patients.[1,2]

The goals of the antibiotic regimens used to treat diabetic lower-extremity infections are to cure the infection or prevent its further spread until debridement or other surgical intervention can take place.[3] In more severe cases (eg, exposed bone, recurrent/chronic infections), the cornerstones of initial treatment are surgery along with the use of potent intravenous antimicrobial therapy.[3]

The bacterial flora of the diabetic lower-extremity infection include normal skin flora such as staphylococci and streptococci, gram-negative aerobes (Enterobacteriaceae), and gram-negative anaerobes, including *Bacteroides fragilis*. *Pseudomonas aeruginosa* is generally not pathogenic in these infections.[4] As fewer antimicrobial agents are appearing on the market, rational application of currently available agents, including beta-lactam/beta-lactamase–inhibitor combinations, is of primary importance.[5–10] However, these combination products often have the disadvantages of frequent dosing, poor penetration into infected tissues, and greater expense; furthermore, they have been implicated in contributing to the promotion of bacterial resistance, including vancomycin B resistance in enterococci.[11,12]

Ceftriaxone (CTX) is a broad-spectrum third-generation cephalosporin that is effective against most aerobes, both gram positive and gram negative, and has some activity against gram-negative anaerobes commonly found in diabetic lower-extremity infections.[13–16] Metronidazole (MTZ) has excellent antianaerobic activity, particularly against *B fragilis*.[17] Its marked concentration-dependent killing and prolonged postantibiotic effect support the hypothesis that dosing every 6 hours is unnecessary, with administration every 12 hours sufficient for a 0.5-g dose and every 24 hours for a 1-g dose.[18–20] Previous studies of the combination of the 2 agents in vitro and in healthy volunteers found that CTX maintained serum bactericidal titers of at least 1:4, and MTZ concentrations remained above the minimum inhibitory concentration for *B fragilis*.[19] The aforementioned dosing strategy is supported by the results of retrospective clinical studies of this combination.[21,22]

This study compared the efficacy, tolerability, and cost differences associated with the use of MTZ plus CTX given once daily with those of ticarcillin/clavulanate potassium (T/C) given every 6 hours, the standard of care at the time the study was conducted, in hospitalized older males with diabetic lower-extremity infections.

PATIENTS AND METHODS

This prospective, randomized, open-label study was conducted at the Veterans Affairs Medical Center, Kansas City, Missouri. Eligible patients were hospitalized adult males (age ≥18 years) with a diagnosis of type 1 or type 2 diabetes and a clinical diagnosis of a diabetic lower-extremity infection that the referring physician judged likely to be caused by bacteria known or suspected to be susceptible to MTZ/CTX or T/C. The diagnosis was based on physical signs of infection. The presence of at least 2 of the following infection characteristics was required: (1) local heat; (2) purulent drainage from a wound; (3) erythema; (4) body temperature ≥100.6°F; and (5) stage 1, 2, or 3 ulcer severity on a 5-point modified Wagner scale[23] (**Table I**). These are similar to previously published criteria for the clinical diagnosis of diabetic lower-extremity infections.[2,7,23]

Other criteria that were considered as supporting the diagnosis included a white blood cell (WBC) count ≥10,000/mm^3, the presence of >5% banded neutrophils, isolation of organism(s) from bacterial culture, and pain and/or edema at the infection site(s). None of these were criteria for study enrollment or randomization, however.

Exclusion criteria included bone involvement, either suspected or confirmed by radiology (eg, bone scan, radiograph); hypersensitivity to any of the study medications; receipt of an intravenous antibiotic for >24 hours before study enrollment; or presence of neutropenia (neutrophil count ≤1000/mm^3) or thrombocytopenia (platelet count ≤50,000/mm^3). The use of oral antibiotics before hospitalization was not controlled.

This study was approved by both the University of Missouri–Kansas City Institutional Review Board and by the Kansas City Veterans Affairs Medical Center Human Studies and Research and Development committees. All patients provided written informed consent before study entry.

Treatment Regimens

Through the use of a computer-generated schedule, patients were randomized to receive either MTZ 1 g IV

Table I. Staging criteria for diabetic lower-extremity infections.[9] (Patients with stage 1–3 foot infection were eligible for participation in the present study.)

Stage 0	No appreciable infection
Stage 1	Mild infection primarily involving the superficial skin layer (cellulitis)
Stage 2	Mild to moderate infection involving the dermis and epidermis, with infectious involvement through one or both of these layers; possible loculated pus; no fistulous track; no gangrenous tissue
Stage 3	Moderate to severe infection with ulceration and fistulous track formation; muscle tissue involvement; pus formation (loculated and/or exudative); possible limb-threatening infection, including necrotizing fasciitis and/or gangrenous tissue
Stage 4	Severe infection involving bone as well as skin/soft tissue; septicemia; tissue gas and crepitus

plus CTX 1 g IV q24h, each cumulatively run over 90 minutes, or T/C 3.1 g IV q6h, run over 30 minutes. If renal dysfunction was present, doses were adjusted based on creatinine clearance (**Table II**).[24–27]

Therapy was considered to begin at the time of the initial administration of study antibiotic. The end of therapy was considered to occur when a noninvestigator physician noted resolution of the infection and discontinued study antibiotics; the route of antibiotic administration was switched from intravenous to oral; the antibiotics were changed to different intravenous antibiotics; or the patient was discharged.

Clinical and Laboratory Measures

Demographic and anthropometric characteristics (including age, sex, and body weight), the date of the diagnosis of diabetes, and the presence of complications of diabetes, hypertension, and cardiac risk factors were assessed at baseline. Clinical and laboratory data obtained at baseline and before administration of study antibiotics were body temperature, fasting finger-stick blood sugar (FSBS), serum sodium, potassium, blood urea nitrogen (BUN), creatinine, complete blood count (CBC) with automated differential, and swab of the infected area.

The patient's provider or study personnel staged the wound at baseline and daily throughout the study. To maintain consistency, the same evaluator graded the wound daily for the duration of the study. Other daily evaluations included the maximum temperature recorded in the previous 24 hours, morning FSBS, and serum sodium, BUN, and creatinine concentrations. A CBC with differential and serum sodium and potassium concentrations were obtained and wound staging was performed 96 hours after study enrollment and at the end of the study (if applicable).

Outcome Measures

Treatment outcome was determined at or before 96 hours after enrollment and again at the end of study therapy (or at discharge or a change to oral antibiotics). The outcome criteria were consistent with previously published criteria.[28] To be considered a treatment success, the patient must have demonstrated at least 1 of the following measures of clinical stability or improvement at 96 hours: (1) body temperature <100.6°F; (2) normalization of FSBS; (3) improvement in wound staging; or (4) WBC count <10,000/mm^3. Patients who completed <96 hours of study treatment (because they were switched to oral therapy due to significant improvement or were discharged from the hospital) were considered to have been successfully treated if this was noted in the patient's chart by the nonstudy provider. The final treatment outcome was based on the nonstudy provider's discharge assessment of the efficacy of study treatment.

Treatment failure at 96 hours was defined as: (1) a worsening of any of the initial signs and symptoms of

Table II. Adjustment of the doses of study drugs in patients with renal dysfunction.[24–27]

		Creatinine Clearance, mL/min				
Drug	Usual Dose	31–50	21–30	11–20	≤10	Peritoneal Dialysis
Ceftriaxone	1 g q24h	1 g q24h	1 g q24h	1 g q24h	500 mg q24h	500 mg q24h
Metronidazole	1 g q24h	1 g q24h	1 g q24h	1 g q24h	250 mg q24h	250 mg q24h
Ticarcillin/clavulanate	3.1 g q6h	3.1 g q6h	3.1 g q8h	3.1 g q12h	3.1 g q12h + 1 dose	3.1 g q12h after dialysis

the diabetic lower-extremity infection after receipt of 1 dose of study medication; (2) the physician's change or addition of at least 1 more intravenous antibiotic to the assigned regimen; or (3) the occurrence of an adverse event requiring discontinuation of study drug at any time after administration of at least 1 dose of study medication. Failure after 96 hours was based on the nonstudy provider's notation of failure or a change of antibiotic based on wound culture results. Patients in whom treatment had been successful initially could be classified as final treatment failures if, after 96 hours, further intravenous antibiotics were added, assessment of wound microbiologic data resulted in a switch of antibiotics, or the nonstudy provider determined that the lower-extremity infection had become worse.

Tolerability

Patients were assessed daily by nonstudy providers for as long as they received study medications to determine whether there had been any adverse events that were attributable to the study medications. Any serious adverse event related to study medication resulted in the patient's immediate withdrawal from the study. Creatinine clearance was calculated daily to determine whether a change in dosing frequency was warranted.

Costs

Medication acquisition costs (Kansas City Veterans Affairs contract prices) for study antibiotics were used in calculating the costs of the regimens in each treatment arm. For the total costs per treatment arm, the mean duration of treatment in days for each regimen was multiplied by the daily cost of the regimen for all patients in each treatment group. Medication preparation and delivery costs were not included. If any interventions were needed to manage adverse events related to study medications, the costs of these interventions were included as well.

Statistical Analysis

Interval-scaled data were analyzed using between-group and within-group (repeated-measures) analysis of variance. Data were collected at regular intervals throughout the study, and the time between the baseline observation and the final observation differed according to patients' response to the assigned treatment regimen. Only the baseline and final observations for each patient were used to analyze treatment effects. When applicable, SPSS version 12.0 (SPSS Inc., Chicago, Illinois) was used. Categorical data were analyzed using the Fisher exact test or chi-square test as appropriate. A 2-tailed P of <0.05 was considered statistically significant.

RESULTS

Seventy patients were enrolled in the study; 36 received MTZ/CTX and 34 received T/C. The study population had a mean (SD) age of 63.8 (10.8) years, a duration of diabetes of 12.4 (9.1) years, 0.5 (0.7) diabetes-related comorbidities, and an initial creatinine clearance of 67.1 (26.0) mL/min. The 2 study groups were well matched with regard to their demographic and clinical characteristics (**Table III**), which reflected American Diabetes Association risk factors for the development of lower-extremity infections.[29] Overall, the majority of patients (71%) presented with cellulitis of the foot, with 66% having no distinct lesion. No adverse events were attributed to either study regimen.

At 96 hours, treatment success was achieved in 31 (86%) patients in the MTZ/CTX group and 28 (82%) patients in the T/C group (P = NS). Twenty-six patients were considered successfully treated on the final day of therapy in both the MTZ/CTX group (72%) and the T/C group (76%) (P = NS). The distribution of criteria for treatment success or failure did not differ between groups at either the 96-hour evaluation or the final evaluation by any single primary or secondary sign of infection, combination of signs, or provider assessment. No demographic characteristic, single primary or secondary sign of infection, combination of signs, or infection site proved predictive of response (success or failure) at either the 96-hour or final evaluation.

Results for the clinical end points are summarized in **Table IV**. There were no significant differences in success or failure in terms of any primary or secondary end point or any combination of end points. Both groups had improvements in creatinine clearance from baseline to the final evaluation, with no significant differences between groups, although no significant renal dysfunction had been present at baseline in either group. Wound stage changed minimally over the course of the study (data not shown), and no patient was considered a treatment success based on wound staging. In patients who achieved treatment success, the mean (SD) duration of study medication was 6.7 (3.3) days in the MTZ/CTX group and 6.1 (4.3) days in the T/C group (P = NS). The direct drug costs for the daily regimens of MTZ/CTX and T/C used in this study were $18.71 and $30.56, respectively. Based on these costs and the mean duration of therapy, MTZ/CTX was associated with savings of $61.06 per hospital admission, or $2198.05 for all patients who received this combination.

Table III. Baseline demographic and clinical characteristics.

Variable	Metronidazole + Ceftriaxone (n = 36)	Ticarcillin/Clavulanate (n = 34)	P
Age, mean (SD), y	65 (11.5)	62 (9.9)	0.292
Male, no. (%)	36 (100)	34 (100)	1.000
Duration of diabetes, mean (SD), y	10.5 (7.9)	13.9 (9.8)	0.173
Creatinine clearance, mean (SD), mL/min	68.4 (28.5)	65.7 (23.4)	0.682
Comorbidities, no. (%)			
Hypertension	18 (50)	21 (62)	0.347
Coronary artery disease	14 (39)	11 (32)	0.624
Peripheral artery disease	12 (33)	8 (24)	0.433
Hyperlipidemia	8 (22)	9 (26)	0.783
Diabetic neuropathy	7 (19)	6 (18)	1.000
Chronic renal insufficiency	4 (11)	3 (9)	1.000
Hypothyroidism	4 (11)	0 (0)	0.115
Diabetic retinopathy	3 (8)	2 (6)	1.000
Diabetic nephropathy	1 (3)	1 (3)	1.000
No. of comorbidities, mean (SD)	2.0 (1.6)	1.8 (1.4)	0.571
Site/distribution of infection, no. (%)			
Foot	12 (33)	13 (38)	0.804
Toe	4 (11)	9 (26)	0.129
Unilateral	8 (22)	5 (15)	0.543
Bilateral	3 (8)	0 (0)	0.240
Cellulitis (no distinct lesion)	14 (39)	9 (26)	0.315

Table IV. Results for clinical end points. Values are mean (SD).

Variable	Metronidazole + Ceftriaxone	Ticarcillin/ Clavulanate	P, Between Groups
Temperature, °F			
Baseline	98.9 (1.6)	98.2 (1.2)	0.063
Final	98.2 (0.8)	98.2 (0.9)	0.883
White blood cell count, cells/mm^3			
Baseline	10.3 (4.2)	9.1 (3.2)	0.187
Final	8.6 (3.0)	8.3 (2.9)	0.643
Finger-stick blood sugar, mg/dL*			
Baseline	160.6 (83.8)	159.8 (59.5)	0.971
Final	167.6 (72.6)	162.1 (54.9)	0.723
Creatinine clearance, mL/min†			
Baseline	68.4 (28.5)	65.7 (23.4)	0.682
Final	64.5 (25.9)	70.6 (21.4)	0.414

*n = 22, metronidazole + ceftriaxone; n = 17, ticarcillin/clavulanate.
†n = 18, metronidazole + ceftriaxone; n = 13, ticarcillin/clavulanate with serum creatinine measurements on days 1 and 4.

The microbiology laboratory performed baseline wound swab cultures of samples from 53 patients. Each of 41 cultures grew a mean (SD) of 1.2 (0.4) bacterial pathogens (total of 87 pathogens). Microbiology results did not differ between groups. The most frequently cultured bacteria considered possibly pathogenic were *Staphylococcus aureus* (n = 20), group B streptococci (n = 9), and *Enterococcus faecalis* (n = 6) (**Table V**, **Figure**). *P aeruginosa* was cultured from the wounds of 3 patients (1 MTZ/CTX, 2 T/C) but was considered nonpathogenic; there was no change in antibiotic in any of these cases.

Fifteen patients in the MTZ/CTX group and 12 in the T/C group had a change in antibiotics before the final evaluation (P = NS). These changes were predominantly switches to oral therapeutic equivalents at the time of hospital discharge. Of the 15 patients in the MTZ/CTX group with an antibiotic change, 12 (80%) were considered treatment successes at 96 hours, as were 7 (47%) at the final evaluation. Of the 12 patients in the T/C group with an antibiotic change, a corresponding 9 (75%) and 7 (58%) were considered treatment successes. The differences between groups were not significant.

Table V. Most commonly cultured bacteria that were considered possibly pathogenic, by number of patients.

Organism	Metronidazole + Ceftriaxone	Ticarcillin/ Clavulanate	*P*
Staphylococcus aureus	13	7	0.190
Group B streptococci	7	2	0.152
Coagulase-negative staphylococci	4	1	0.258
Enterococcus faecalis	2	4	0.422

Resistance to study regimens was observed in cultures from 7 patients (4 MTX/CTZ, 3 T/C) due to methicillin-resistant *S aureus* or *Staphylococcus epidermidis*. Six of these 7 patients had a change in antibiotics or addition of an antibiotic. The other patient continued study treatment and was considered a treatment success, as recorded by the nonstudy provider.

DISCUSSION

To the best of our knowledge, this is the first published report of a prospective trial comparing once-daily MTZ/CTX with any other antibiotic or antibiotic combination in patients with diabetic lower-extremity infection. Positive outcomes were observed in patients who received MTZ/CTX; based on multiple measures, the outcomes in the MTZ/CTX group were similar to those in the T/C group. The proportion of responders to T/C in this study is similar to rates reported in the literature, including those for regimens containing fluoroquinolones.[8,30–32]

A high proportion of patients met the criteria for treatment success within 96 hours of starting therapy. There were no between-group differences in the proportion of patients achieving treatment success or in the mean time to treatment success. Both drug combinations were well tolerated, with no adverse events in either treatment group that were attributed to study medications by noninvestigator physicians.

Despite the excellent anaerobic coverage and low acquisition cost of MTZ, treatment guidelines for diabetic lower-extremity infection narrowly incorporate its use as a therapeutic alternative.[33] The results of the present study suggest that once-daily MTZ/CTX, when dosed at extended intervals, may be as effective against polymicrobial infections as T/C. This is supported by the results of comparisons in patients with mixed infections that indicated the equivalence of

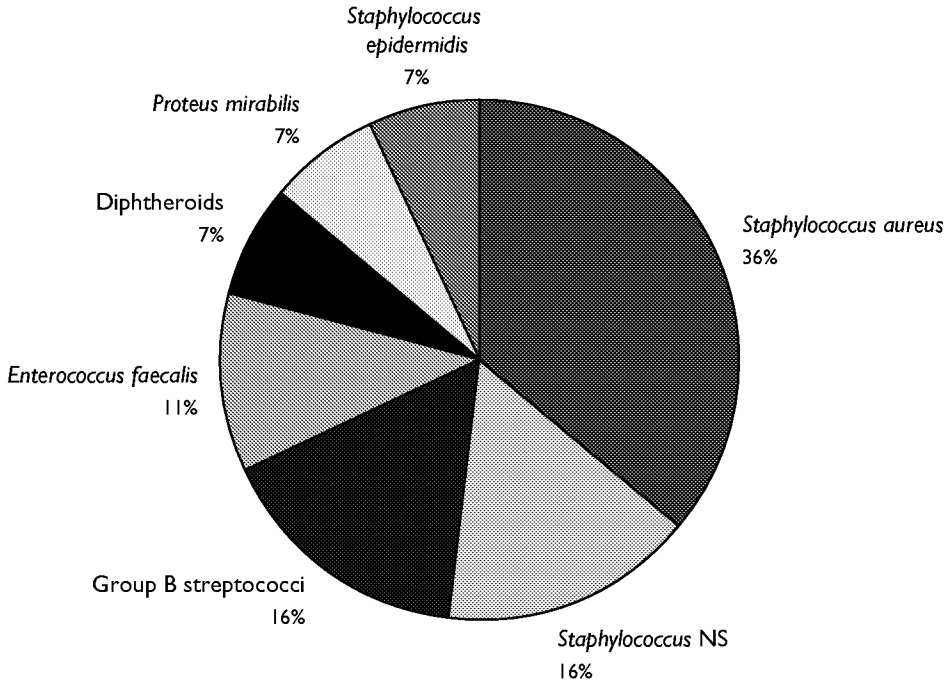

Figure. Distribution of the 87 pathogens isolated during the study. NS = not specified.

MTZ/CTX to ertapenem,[34] ciprofloxacin/MTZ,[35] and cefotaxime.[36]

Approximately half of all diabetic lower-extremity infections require hospital-based intervention, accounting for 80% of total treatment costs for patients with this diagnosis.[37] The once-daily MTZ/CTX regimen described in this article is less labor intensive than T/C, which is administered 4 times daily. The potential for cost savings, which is consistent with data from a previous report,[38] may be greater if alternative drug-delivery methods are used.[38–40]

The lack of adverse events attributable to either study regimen is not totally unexpected. All agents used in this study are known to be well tolerated and have been reported to be associated with minimal or no adverse events in clinical studies of higher doses and greater durations of therapy.[41,42]

This was an open-label comparison of MTZ/CTX with T/C, a recommended antibiotic for the empiric treatment of limb-threatening infections.[21] Because the study was not blinded, there may have been a potential for bias; however, efficacy was evaluated using several objective measures, including improvement in WBC count or FSBS, and normalization of body temperature. Wound size was measured by nonstudy personnel in 67 patients and by a study investigator in 3 patients. A wound culture was obtained when the nonstudy provider deemed it appropriate, but this proved not to be of benefit in many cases. The study requirement that culture of a swab from the infected site be compared with a deep-wound culture made the microbiologic results less reliable than they might have been had biopsy been used. Surgical debridement is part of the standard treatment of limb-threatening infections. In the present study, we assumed that surgical debridement occurred as necessary rather than determining its occurrence or role in efficacy outcomes, and we did not assess the prevalence of debridement in either study arm, a possible uncontrolled bias. This study was conducted at a Veterans Affairs Medical Center and, although female patients were not excluded, only male patients were enrolled. These patients typically present with several comorbid conditions that may or may not be present in women. Although applying the results of this study to the general population with diabetic lower-extremity infections may not be appropriate, many characteristics of the population in this study (duration of diabetes, sex, glycemic control, and comorbid conditions) are in line with risk factors for diabetic lower-extremity infections recognized in consensus guidelines.[29]

CONCLUSION

In this population of older males, an empiric regimen of once-daily MTZ/CTX was as well tolerated and effective as T/C in the treatment of diabetic lower-extremity infections and was associated with reduced institutional costs.

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Address correspondence to: Patrick G. Clay, PharmD, Assistant Professor of Pharmacy Practice, Department of Pharmacy Practice, University of Missouri–Kansas City School of Pharmacy, 2411 Holmes Street, M3-C19, Kansas City, MO 64108–2792. E-mail: claypg@umkc.edu